Toxic Response of the Kidney

KIDNEY FUNCTION

- *A WET BED* aids in memory of kidneys functions :
  - A – maintaining ACID-base balance
  - W – maintaining WATER balance
  - E – ELECTROLYTE balance
  - T – TOXIN removal
  - B – BLOOD Pressure control
  - E – making ERYTHROPOIETIN
  - D – Vitamin D metabolism

KIDNEY PHYSIOLOGY

- There are 3 anatomical areas in the kidney :

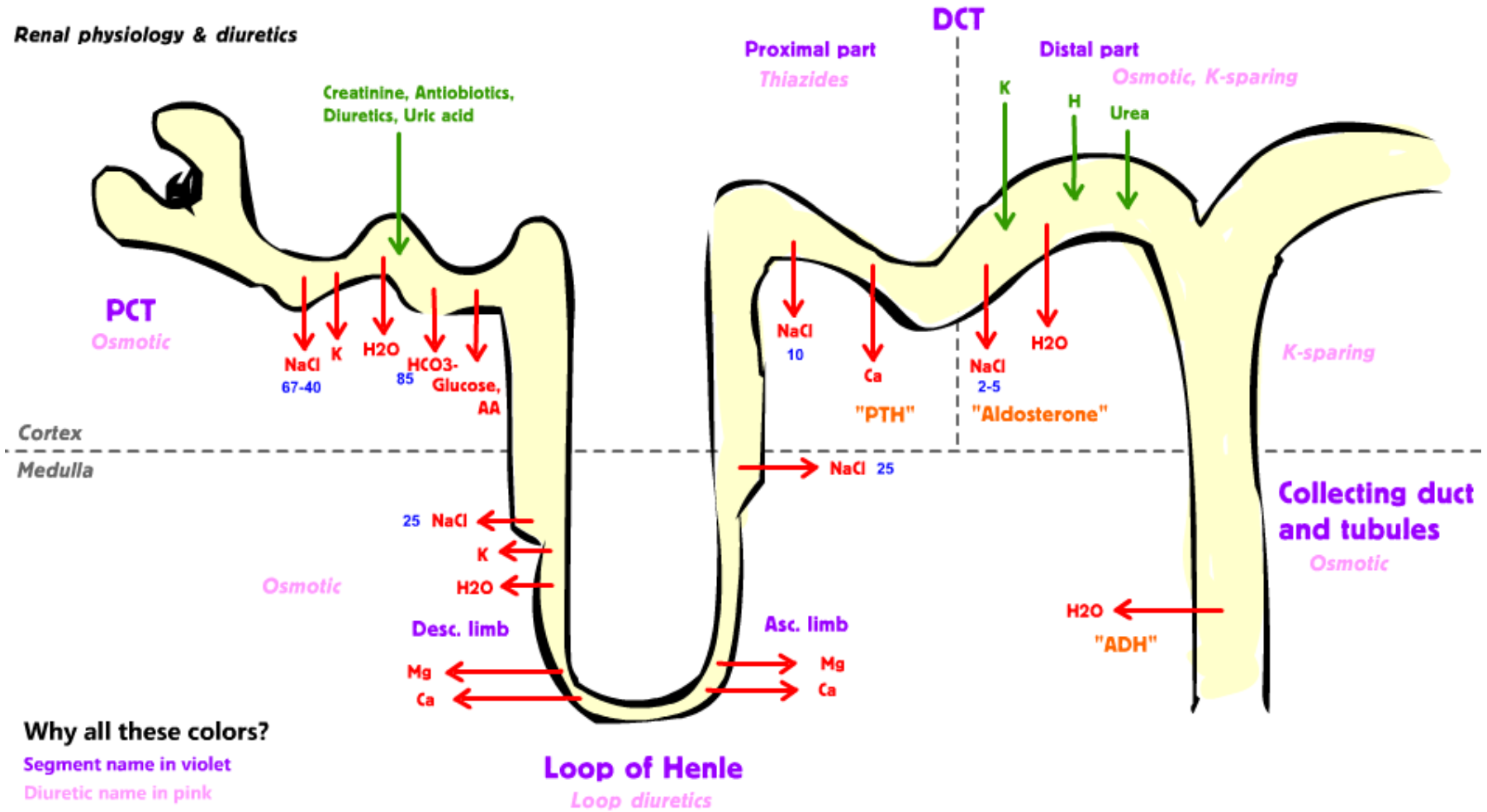
- *Cortex*
- *Medulla*
- *Papilla*

- The cortex constitutes the major portion of the kidney and receives a disproportionately higher percentage (90%) of blood flow compared to the medulla (6%–10%) or papilla (1%–2%)
- When a blood – borne toxicant is delivered to the kidney, a high percentage of the material will be delivered to the cortex and will have a greater opportunity to influence cortical rather than medullary or papillary functions.
- Medullary and papillary tissues are exposed to higher luminal concentrations of toxicants for prolonged periods of time, a consequence of the more concentrated tubular fluid and the more sluggish flow of blood and filtrate in these regions.

The Nephron

- The functional unit of the kidney, the nephron, may be considered in three portions: *the vascular element, the glomerulus, and the tubular element.*
- All nephrons have their primary vascular elements and glomeruli in the cortex.
- The proximal convoluted tubule is localized in the cortex and sends the pars recta (straight portion) of the proximal tubule and loops of Henle deep into the substance of the kidney.

KIDNEY PHYSIOLOGY



Why all these colors?

Segment name in violet

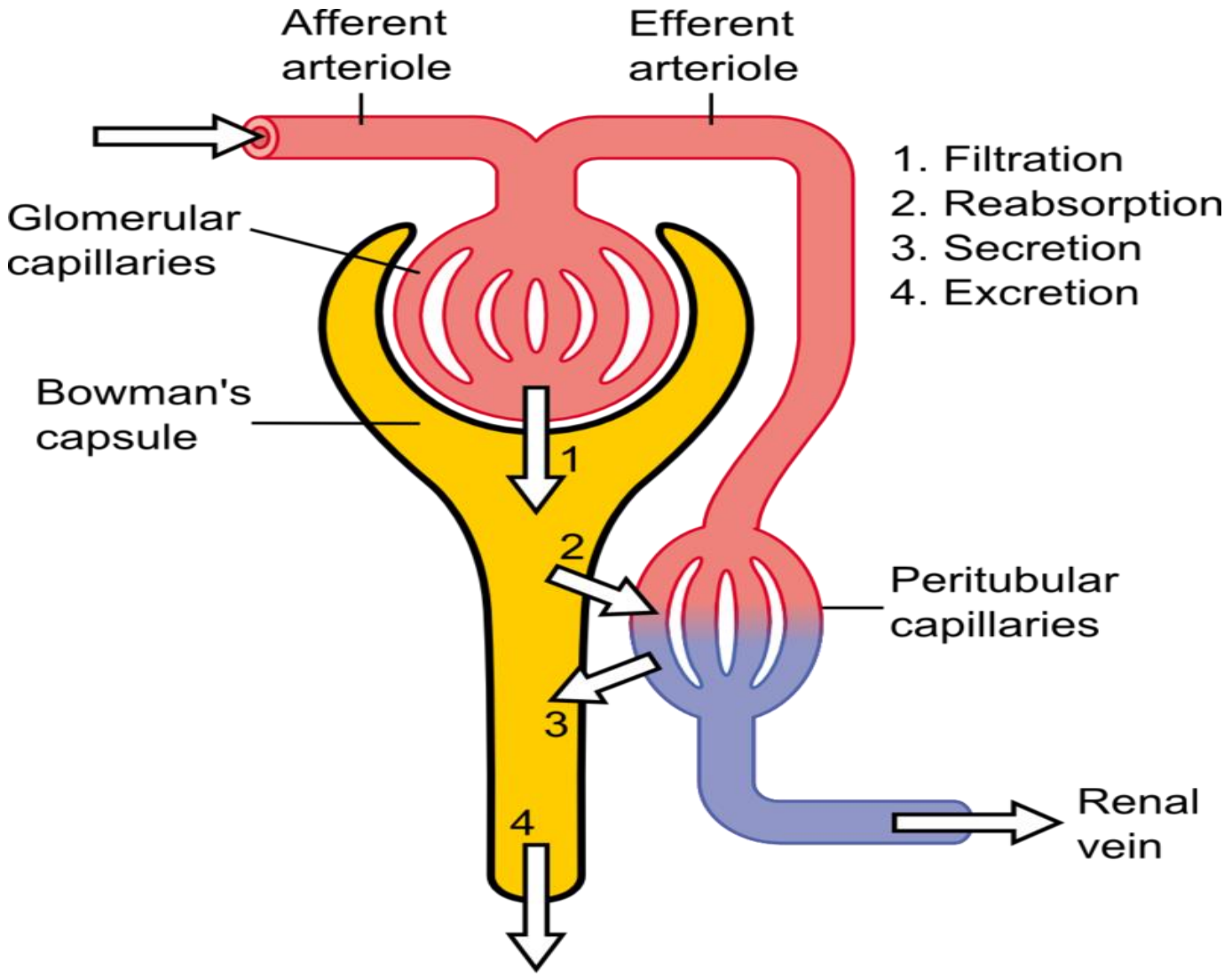
Diuretic name in pink

Reabsorption in red

Secretion in green

Percentage in blue

Hormone in orange



Excretion = Filtration – Reabsorption + Secretion

- Injury to the vasculature, glomeruli, tubules, or interstitium can lead to renal dysfunction which then lead to a decrease in glomerular filtration.
- As the kidneys fail, serum concentrations of the marker substances urea and creatinine increase.
- By the time blood urea nitrogen (BUN) or serum creatinine exceeds the upper limit of normal, GFR is reduced by more than 50%.

- Many xenobiotics cause or aggravate renal dysfunction. The kidneys are particularly susceptible to toxic injury for four reasons:

1. They receive 20% to 25% of cardiac output of blood
2. They contain enzymes leading to form an active metabolite such as in case of APAP
3. They remove water from the filtrate and may build up a high concentration of xenobiotics
4. The glomeruli and interstitium are susceptible to attack by the immune system

Mechanisms of nephrotoxicity

- Interaction with receptors
- Inhibition of oxidative phosphorylation
- Disturbance of Ca2+ homeostasis
- Disruption of plasma and subcellular membrane functions

Major Toxic Syndromes of the kidney " Types of nephrotoxicity "

Acute kidney injury	Nephrotic syndrome	Chronic renal disease
Rapidly increasing azotemia	Proteinuria, hypoalbuminemia, edema	Slowly increasing azotemia
Acute prerenal failure Acute urinary obstruction Acute tubular necrosis Acute interstitial nephritis	Minimal glomerular change Membranous nephropathy Focal segmental glomerulosclerosis	Chronic interstitial nephritis Papillary necrosis Chronic glomerulosclerosis

Chronic kidney disease

- It refers to a disease process that causes progressive decline of renal function over a period of months to years.
- There is usually a gradual rise in BUN and serum creatinine concentration as glomerular filtration falls. There is no symptoms other than nocturia
- The most common lesion of chronic kidney disease due to nephrotoxic substances is chronic interstitial nephritis which involves destruction of tubules over a prolonged period , with tubular atrophy, fibrosis, and a variable cellular infiltrate, sometimes accompanied by papillary necrosis.

Chronic kidney disease

- Interstitial nephritis is characterized by failure of the diseased tubules to adapt to the renal impairment, resulting in metabolic imbalances such as hyperchloremic metabolic acidosis, sodium wasting, and hyperkalemia early in the disease course.
- Injury to erythropoietin secreting cells may produce a disproportionate anemia.
- Chronic interstitial nephritis can be caused by lithium and ciclosporin

Nephrotic syndrome

- It is characterized by massive proteinuria *(> 3 g/d in the adult),* hypoalbuminemia, hyperlipidemia, and edema
- The underlying event is injury to the glomerular barrier that normally prevents macromolecules from passing from the capillary lumen into the urinary space.
- Xenobiotics induce nephrotic syndrome in two ways :

➢ They may release hidden antigens into the blood, which leads to antigen–antibody complex formation after the immune response is elicited. These complexes subsequently deposit in the glomerular basement membrane, thereby changing its consistency (such as gold)

➢ They can upset the immunoregulatory balance (such as NSAIDs)

Xenobiotics that cause nephrotic syndrome

Antimicrobials (rifampicin, cefixime)
Captopril
Drugs of abuse (heroin, cocaine)
Insect venom
Interferon α
Metals (gold, mercury, lithium)
NSAIDs
Penicillamine

Acute kidney injury (AKI)

- It is an abrupt decline in renal function that impairs the capacity of the kidney to maintain metabolic balance.
- The three main categories of acute kidney injury are :
  - Prerenal
  - Postrenal
  - Intrinsic

Prerenal failure

- It occurs due to impaired renal perfusion, which can occurs with : volume depletion, systemic vasodilatation, heart failure, or pre – glomerular vasoconstriction
- Toxic events for prerenal failure include :

- Bleeding (overdose of anticoagulants)
- Volume depletion (diuretics, cathartics, or emetics)
- Cardiac dysfunction (β-adrenergic antagonists)
- Hypotension from any cause

POSTRENAL FAILURE

- It can be occur due to :
  - Urinary tract obstruction
  - Blocked urinary flow
- In postrenal failure, there is a tubular dilation, predominantly in the distal nephron segments (ie, the collecting ducts and distal tubules), occurs initially and glomerular structure is preserved, subsequently dilation of the Bowman space occurs, and finally peri-glomerular fibrosis develops.
- GFR falls as tubule pressure counteracts the capillary hydraulic pressure gradient. Subsequently there is a fall in renal perfusion leading to ischemic damage to nephrons.
- Tubular function is impaired such that concentrating ability, potassium secretory function, and urinary acidification mechanisms are all altered.

Xenobiotics associated with post renal failure

- **Bladder dysfunction :**
  - Anticholinergics
  - Antipsychotics
  - Bromocriptine
  - CNS depressants

- **Crystal deposition :**
  - Acyclovir (IV)
  - Ethylene glycol
  - Fluoroquinolones
  - Methotrexate
  - Sulfonamides
  - Florinated anesthetics

Intrinsic renal failure

Acute tubular necrosis

- It is the most common nephrotoxic event, characterized pathologically by patchy necrosis of tubules, usually the proximal segments.
- The lesion is associated with three different processes:

- Direct toxic injury
- Ischemic injury
- Pigmenturia

- Direct acting xenobiotics affect different segments of the renal tubules; for example :
  - Uranium attacks the proximal tubule
  - Amphotericin attacks the distal tubule
- Ischemic tubular necrosis occur if hypotension or cardiac failure causes ischemia of nephron segments (proximal straight tubule and inner medullary collecting duct) that are particularly vulnerable to hypoxia.

PIGMENTURIA

- Pigmenturia refers to :

- *Myoglobinuria* from rhabdomyolysis (skeletal muscle necrosis)
- *Hemoglobinuria* from massive hemolysis of RBCs (hemolytic anemia)

➢ It can be caused by acute lead poisoning and arsenic toxicity

Xenobiotics associated with rhabdomyolysis leading to myoglobinuria

Statins and fibrates	Especially cerivastatin. Previous chronic kidney disease and hypothyroidism increase the risk of myopathy due to statins. It is also more common in the elderly, those who are severely disabled, and when statins are used in combination with particular other medicines, such as ciclosporin
Antipsychotics	May cause neuroleptic malignant syndrome, which can cause severe muscle rigidity with rhabdomyolysis and hyperpyrexia
NMB	Succinylcholine causes malignant hyperthermia
SSRIs	They cause serotonin syndrome
Diuretics	Hypokalemia

Xenobiotics associated with acute tubular necrosis (ATN)

Acetaminophen	
Antimicrobials :	Aminoglycosides, Amphotericin , Tenofovir, cidofovir
Antineoplastics :	Cisplatin , Ifofamide, Methotrexate
Glycols :	Ethylene glycol , Diethylene glycol
Metals :	Arsenic , Bismuth, Chromium, Mercury, Uranium
Pigments :	Myoglobin and Hemoglobin
Fluorinated anesthetics	
Halogenated hydrocarbons	
Mushrooms :	Amanita smithiana

Acute interstitial nephritis (AIN)

- It is clinically similar to acute tubular necrosis and often must be diagnosed by renal biopsy, which shows a cellular infiltrate separating tubular structures
- All acute interstitial nephritis is caused by hypersensitivity.
- Finding eosinophils in the urine is consistent with this disorder.
- Approximately 25% of patients with xenobiotic – induced interstitial nephritis have no signs of hypersensitivity.
- Unlike those with tubular necrosis, most patients with acute interstitial nephritis have hematuria and leukocyturia, particularly eosinophiluria
- The lesion usually improves after the xenobiotic is removed
- Corticosteroids may hasten recovery

Xenobiotics associated with acute interstitial nephritis

- Allopurinol
- Antimicrobials
- β – Lactams, especially ampicillin
- Methicillin, penicillin
- Rifampin
- Sulfonamides (including mesalamine)
- Vancomycin
- Proton-pump inhibitors
- Azathioprine
- NSAIDs

Acute glomerulonephritis

- It is not common
- Glomerular lesions occur primarily through immune – mediated pathways rather than through direct drug toxicity.
- Heroin and Pamidronate are known to cause focal segmental glomerulosclerosis
- Gold salts therapy can cause membranous nephropathy
- Penicillamine

Aminoglycosides Nephrotoxicity (Mostly Gentamicin)

- Acute nephrotoxicity is reversible, but it may be fatal.
- The risk of nephrotoxicity can be affected by the dose, frequency, duration of therapy, and concurrent use of certain medications such as *NSAIDs, diuretics, cisplatin, ciclosporin, cephalosporin, amphotericin, iodide contrast media, and vancomycin*

Mechanism of aminoglycoside nephrotoxicity

- Enhance generation of superoxide and hydrogen peroxide by renal cortical mitochondria and their interaction leading to generation of hydroxyl radical
- Release of iron from cortical mitochondria leading to enhance generation of hydroxyl radical

Amphotericin B nephrotoxicity

- Mechanism of nephrotoxicity include :

➢ Direct toxicity :

1. Amphotericin inserts into cell membranes, creating pores that increase cell permeability, leading to hypokalemia, hypomagnesaemia, distal RTA.
2. Vasoconstriction of afferent arterioles

➢ Indirect toxicity :

Decreased GFR via tubuolglomerular Feedback mediated vasoconstriction

Analgesic nephrotoxicity

- The specific kidney injuries induced by analgesics are renal papillary necrosis and chronic interstitial nephritis.
- *Mechanism of toxicity :* result from decreased blood flow to the kidney, rapid consumption of antioxidants, and subsequent oxidative damage to the kidney

Nephrotoxic effects of metals

	ATN	AIN	CIN	NS
Arsenic	+++	+	+	
Cadmium			+++	
Chromium	+++			
Gold	+			+++
Iron			+	
Lead	+		+++	
Lithium	+		++	+
Mercury	+++			+
Thallium	+			

Tests for renal function

- Acute :

- To differentiate prerenal failure from acute tubular necrosis:

1. BUN – to – creatinine ratio ; usually > 20 : 1 in prerenal failure
2. Urine Na + usually < 20 mEq/L in prerenal failure; usually > 40 mEq/L in acute tubular necrosis
3. Fractional Na + excretion (FE Na) is most reliable test: ,

$$FE_{Na} = \frac{\text{Urine[Na] / Plasma [Na]}}{\text{Urine[Cr] / Plasma [Cr]}} \times 100$$

- FE Na < 1% (ie, normal) in prerenal failure, if the patient has not received diuretics or large infusions of sodium, which increase Na + excretion despite normal tubular function. In tubular necrosis or interstitial nephritis, renal Na + absorption is decreased, and FE Na > 1%. This is useful except in pigmenturic or iodinated radiocontrast – associated renal failure, when the test is of no benefit.